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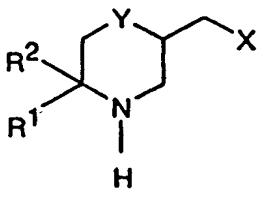
(54) Title: (THIO)MORPHOLINE–SUBSTITUTED CARBOXYLIC AND PHOSPHINIC ACIDS

(57) Abstract

A compound of formula (I), wherein X is carboxy or a group of formula –PO(OH)–R where R is an unsubstituted or substituted hydrocarbyl group, R^1 is a monovalent aromatic or araliphatic group connected through a carbon atom thereof to the indicated carbon atom, R^2 is hydrogen or an unsubstituted or substituted hydrocarbyl group, and Y is oxygen or sulphur when X is carboxy, or sulphur when X is –PO(OH)–R, or a salt or ester thereof. Compound I is useful in the treatment or prevention of a condition characterized by stimulation of a $GABA_B$ receptor.



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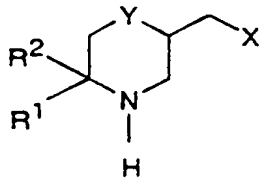
(THIO)MORPHOLINE-SUBSTITUTED CARBOXYLIC AND PHOSPHINIC ACIDS

This invention relates to chemical compounds which are substituted carboxylic or phosphinic acids, or salts or esters thereof, their preparation and their use as pharmaceuticals.

Carboxylic and methylphosphinic acids with $GABA_B$ antagonistic properties are known from WO 94/22843. It has now been found that compounds having remarkably high $GABA_B$ receptor binding affinity can be provided by preparing novel substituted carboxylic and phosphinic acids containing a morpholine or thiomorpholine ring.

In a first aspect the present invention provides compounds of formula



(I)

or salts or esters thereof,

wherein X is carboxy or a group of formula -PO(OH)-R where R is an unsubstituted or substituted hydrocarbyl group. R^1 is a monovalent aromatic or araliphatic group connected through a carbon atom thereof to the indicated carbon atom. R^2 is hydrogen or an unsubstituted or substituted hydrocarbyl group, and Y is oxygen or sulphur when X is carboxy, or sulphur when X is -PO(OH)-R.

R^1 as an aromatic group may have up to 40 carbon atoms and may be an aryl group such as a phenyl, tolyl, xylyl or naphthyl group or a heterocyclic aromatic group such as a thienyl, furyl, indolyl or pyridyl group, which groups may be unsubstituted or substituted by one or more substituents such as halogen, hydroxy, C_1 to C_4 alkoxy, carboxyl, esterified or amidated carboxyl, cyano, carboxy-C_1-C_6 alkyl, esterified or amidated carboxy-C_1-C_8 alkyl, cyano-C_1-C_8alkyl or nitro.

Preferably R^1 as an aromatic group is an aryl group of 6 to 15 carbon atoms which may be unsubstituted or substituted in one or more positions by halogen, carboxyl, esterified or amidated carboxyl, cyano, carboxy-C_1-C_8 alkyl, esterified or amidated carboxy-C_1-C_8 alkyl, cyano-C_1-C_8 alkyl

or nitro, or R^1 as an aromatic group is a 5 to 10-membered heterocyclic aromatic group having one or two nitrogen atoms in the ring system. More preferably, R^1 as unsubstituted or substituted aryl is phenyl or phenyl substituted in one or more of the meta and para positions, with respect to the carbon atom thereof linked to the indicated (thio)morpholine ring, by halogen, carboxyl, esterified or amidated carboxyl, cyano or nitro. More preferably, R^1 as a heterocyclic aromatic group is a 5 to 10-membered heterocyclic group having a nitrogen atom as the only ring hetero atom.

R^1 as an araliphatic group may have 7 to 40 carbon atoms and may be phenyl-lower alkyl, for example benzyl or 2-phenylethyl, α, α-diphenyl-lower alkyl such as diphenylmethyl or α-naphthyl-lower alkyl such as naphthylmethyl, any of which groups may be unsubstituted or substituted in one or more positions, which may be ortho, meta or para positions, by a substituent chosen from those hereinbefore specified for R^1 as an aromatic group. Preferably, R^1 as an araliphatic group is α-phenyl-C_1-C_4 alkyl, which is unsubstituted or substituted in one or more positions by halogen, carboxyl, esterified or amidated carboxyl, cyano or nitro.
In especially preferred carboxylic acids of the invention and their salts and esters, R^1 is phenyl, 3-bromophenyl, 3-iodophenyl, 3, 4-dichlorophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-(methoxycarbonyl)phenyl, 3-(ethoxycarbonyl)phenyl, 3-nitrophenyl, benzyl, 3-carboxybenzyl, 3-ethoxycarbonylbenzyl, 4-iodobenzyl, 4-carboxybenzyl, 4-ethoxycarbonylbenzyl or indol-3-yl.

In especially preferred phosphinic acids and their salts and esters, R^1 is 3-bromophenyl, 3-carboxyphenyl or 3-(methoxycarbonyl)phenyl.

R as an unsubstituted or substituted hydrocarbyl group may, in general, have 1 to 40 carbon atoms.

Aliphatic radicals R are, for example, lower alkyl, lower alkenyl, lower alkynyl, oxo-lower alkyl, hydroxy- or dihydroxy-lower alkyl, hydroxy-lower alkenyl, mono-, di- or poly-halo-lower alkyl, mono-, di- or poly-halo-lower alkenyl, mono-, di- or poly-halo(hydroxy)-lower alkyl, mono-, di- or poly-halo(hydroxy)-lower alkenyl, lower alkoxy-lower alkyl, di-lower alkoxy-lower alkyl, lower alkoxy(hydroxy)-lower alkyl, lower alkoxy(halo)-lower alkyl, lower alkylthio-lower alkyl and di-lower alkylthio-lower alkyl.

Cycloaliphatic radicals R are, for example, cycloalkyl, hydroxycycloalkyl, oxa-, dioxa-, thia- and dithia-cycloalkyl.

Cycloaliphatic-aliphatic radicals R are, for example, cycloalkyl-lower alkyl, cycloalkenyl-lower alkyl, cycloalkyl(hydroxy)-lower alkyl and (lower alkylthio)cycloalkyl(hydroxy)-lower alkyl.

Araliphatic radicals R are, for example, phenyl-lower alkyl radicals that are unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl, preferably α-phenyl-lower alkyl substituted as indicated or unsubstituted α,α-diphenyl- or α-naphthyl-lower alkyl.

Heteroarylaliphatic radicals R are, for example, thienyl-, furyl- or pyridyl-lower alkyl radicals that are unsubstituted or substituted, especially mono- or di-substituted, by halogen, preferably unsubstituted α-thienyl-, α-furyl- or α-pyridyl-lower alkyl.

Hereinbefore and hereinafter, lower radicals and compounds are to be understood, for example, as those containing up to and including 7, preferably up to and including 4, carbon atoms.

In preferred compounds of formula I, R is C_1-C_7alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl, α,α-di-C_1-C_4alkoxy-C_1-C_4alkyl, especially α,α-di-C_1-C_4alkoxy-methyl or ethyl, such as dimethoxy- or diethoxy-methyl or 1, 1-diethoxyethyl, cyano-C_1-C_4 alkyl such as cyanomethyl or 2-cyanoethyl, acylamino-C_1-C_5 alkyl such as acetylaminoethyl, acetylaminopropyl, acetylaminopentyl or benzoylaminomethyl, C_3-C_6-cycloalkyl-C_1-C_4alkyl, such as cyclopropyl- or cyclohexyl-methyl, C_3-C_6cycloalkenyl-C_1-C_4alkyl, such as cyclohex-3-enylmethyl, or is phenyl-C_1-C_4alkyl, such as benzyl, that is unsubstituted or mono-, di- or tri-substituted by C_1-C_4alkyl, such as methyl, C_1-C_4alkoxy, such as methoxy, hydroxy and/or by halogen, such as fluorine, chlorine or iodine.

In more preferred compounds of the invention, R is C_1-C_5 alkyl such as methyl, ethyl or butyl, α,α-di-(C_1-C_4 alkoxy)methyl such as diethoxymethyl, α,α-di-(C_1-C_4 alkoxy)ethyl such as 1, 1-diethoxyethyl, C_3-C_6 cycloalkyl-C_1-C_4 alkyl such as cyclopropylmethyl or cyclohexylmethyl, benzyl or 4-methoxybenzyl. In especially preferred compounds, R is cyclohexylmethyl or 4-methoxybenzyl.

R^2 as an unsubstituted or substituted hydrocarbyl group may have up to 40 carbon atoms and may be a C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_3 to C_8 cycloalkyl, C_4 to C_{13} cycloalkylalkyl, C_6 to C_{10} aryl or C_7 to C_{13} aralkyl group, any of which groups may be substituted by one or more substituents chosen from those hereinbefore specified for R^1. Preferably R^2 is hydrogen, lower alkyl, C_3 to C_6 cycloalkyl, C_6 to C_8 aryl or C_7 to C_9 aralkyl, especially hydrogen or isopropyl.

Specific especially preferred carboxylic acids of the invention and their salts and esters are those in which R^1 is phenyl, 3-bromophenyl, 3-iodophenyl, 3, 4-dichlorophenyl, 3-cyanophenyl, 3-(methoxycarbonyl)phenyl, 3-(ethoxycarbonyl)phenyl, 3-carboxyphenyl, 3-nitrophenyl, benzyl, 4-iodobenzyl, 3-carboxybenzyl, 3-ethoxycarbonylbenzyl, 4-carboxybenzyl, 4-ethoxycarbonylbenzyl or indol-3-yl and R^2 is hydrogen or isopropyl. Most preferred specific compounds are those hereinafter described in the Examples.

Specific especially preferred phosphinic acids of the invention and their salts and esters are those in which R^1 is 3-bromophenyl, 3-(methoxycarbonyl)phenyl or 3-carboxyphenyl, R is cyclohexylmethyl or 4-methoxybenzyl R^2 is hydrogen.

The compounds of formula I may be in the form of internal salts and can form both acid addition salts and salts with bases by conventional salt-forming reactions.

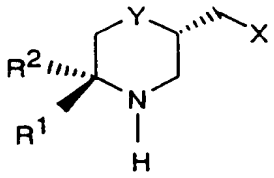
Acid addition salts of compounds of formula I are, for example, their pharmaceutically acceptable salts with suitable mineral acids, such as hydrohalic acids, sulfuric acid or phosphoric acid, for example hydrochlorides, hydrobromides, sulfates, hydrogen sulfates or phosphates, or salts with suitable aliphatic or aromatic sulfonic acids or N-substituted sulfamic acids, for example methanesulfonates, benzenesulfonates, p-toluenesulfonates or N-cyclohexylsulfamates (cyclamates).

Salts of compounds of formula I with bases are, for example, their salts with pharmaceutically acceptable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb, for example alkali metal salts, especially sodium or potassium salts, alkaline earth metal salts, especially calcium or magnesium salts, and also ammonium salts with ammonia or organic amines or quarternary ammonium bases.

As well as forming salts with bases, the acidic group in formula I may also be esterified. Thus, the invention includes compounds of formula I in the form of their esters with an alcohol, which may be a C_1 to C_{10} alkanol in which the alkyl radical is unsubstituted or substituted, for example by halogen, cyano or C_1 to C_4 alkoxy.

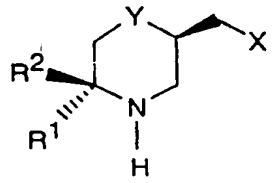
Provided asymmetric carbon atoms are present, the compounds according to the invention may be in the form of isomeric mixtures, especially in the form of racemates, or in the form of pure isomers, especially optical antipodes.

Preferred isomers of compounds of formula I are those in which R^1 and the group attached to the 2-position of the indicated morpholine or thiomorpholine ring are trans with respect to each other, i.e. those of formula



(IA)

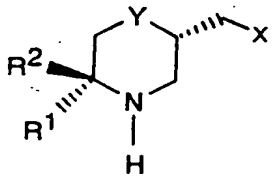
or of formula



(IB)

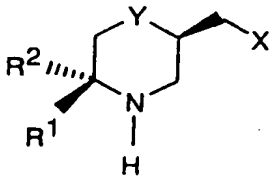
where R^1, R^2, X and Y are as hereinbefore defined.

Other preferred isomers of formula I are those in which R^1 and the group attached to the 2-position of the indicated morpholine or thiomorpholine ring are cis with respect to each other, i.e. those of formula



(IC)

or of formula



(ID)

where R^1, R^2, X and Y are as hereinbefore defined.

It has been found that the compounds of formula I and their pharmaceutically acceptable salts and esters have valuable pharmacological properties. They exhibit an effective binding to the $GABA_B$ receptor and have been found to be antagonists of GABA (γ-aminobutyric acid) at that receptor. With regard to the mechanism, antagonism at $GABA_B$ receptors can increase the release of rapid stimulant amino acid transmitters, that is to say, glutamate and aspartate, and thus improve information processing in the brain. This is in keeping with the finding that the late post-synaptic inhibition potential in the hippocampus, which is attributed to a $GABA_B$ mechanism, is broken down by the antagonists and thus permits a faster nerve impulse transmission sequence.

It has also been found that chronic treatment with anti-depressants and repeated electric shocks increase the number of $GABA_B$ receptors in the cerebral cortex of rats. In accordance with receptor theories, chronic treatment with $GABA_B$ antagonists should have the same effect. For this and other reasons, $GABA_B$ antagonists can accordingly act as anti-depressants.

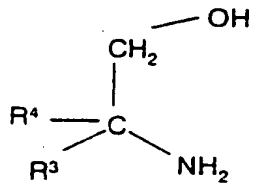
The $GABA_B$ antagonists according to the invention interact at the $GABA_B$ receptor with IC_{50} values from 10^{-7} to 10^{-9} M (mole/litre) on cerebral cortex membranes of rats. In contrast to $GABA_B$ agonists, such as baclofen, they do not potentiate the stimulation by noradrenalin of adenylate cyclase on sections of the cerebral cortex of rats but act as antagonists of the baclofen action. The

antagonists not only exhibit antagonism towards baclofen but also have an independent action as antagonists of endogenous GABA.

In view of their excellent $GABA_B$ antagonistic properties, the compounds of the invention are suitable for use in the treatment or prevention of conditions characterised by stimulation of $GABA_B$ receptors. Thus they are suitable for use as nootropics, antidepressants and anxiolytics, for example in the treatment of central nervous system disorders such as anxiety, depression, cerebral insufficiency, epilepsy of the "petit mal" type, i.e. absence epilepsy in children and adolescents, atypical absences such as the Lennox-Gastant syndrome, in the treatment of conditions requiring enhancement of cognitive performance and as an antidote to baclofen. They are also suitable for use in the treatment of schizophrenia and myopia.

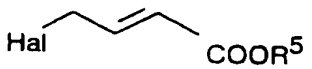
In a further aspect the invention provides a process for the production of the compounds of formula I and their salts and esters.

Compounds of formula I where X is carboxy and Y is oxygen may be prepared by reacting a compound of formula



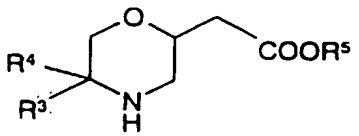
II

where R^3 is R^1 as hereinbefore defined except that R^3 may not be substituted by carboxyl, and R^4 is R^2 as hereinbefore defined except that R^4 may not be substituted by carboxyl, with a compound of formula



III

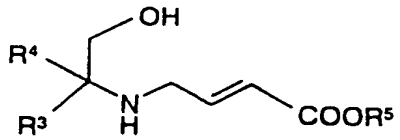
where Hal is halogen, e.g. chlorine or bromine, and R^5 is C_1 to C_8 alkyl, e.g. n-hexyl, n-octyl, preferably C_1 to C_4 alkyl such as methyl, ethyl, isopropyl or isobutyl, especially ethyl, in the presence of a base, to give a compound of formula



IV

where R^3 and R^4 are as defined in formula II, followed, where required, by one or more substitution reactions to change the nature of a substituent in R^3 and/or R^4 and/or by hydrolysis of an ester substituent in R^3 and/or R^4 to carboxyl and/or by hydrolysis of the ester group -$COOR^5$ to carboxyl.

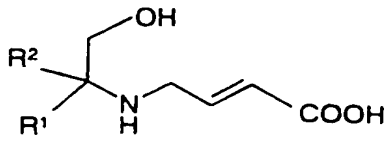
By appropriate selection of the base and reaction conditions, the reaction of compounds of formulae II and III, which proceeds by monoalkylation of the amino group followed by cyclisation, may be effected in a one-step procedure. Preferably, to avoid complications resulting from dialkylation of the amino group, the reaction is carried out in two stages. In the first stage, a weak base, for example a hindered amine such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or a tertiary aliphatic amine such as diisopropylethylamine is added slowly to a mixture of the compounds of formulae II and III in a solvent, preferably a hydrocarbon such as benzene, toluene or xylene, or a halohydrocarbon such as dichloromethane, at a temperature of 0°C to 110°C, to give a novel intermediate product of formula



V

where R^3, R^4 and R^5 are as hereinbefore defined. This intermediate is then treated with a base under harsher conditions than those employed in its formation, for example with a similar base at a higher temperature or, preferably, with a stronger base such as an alkali metal hydride at a temperaure from 0°C to 110°C. The treatment of the intermediate with base may be carried out in a solvent, preferably a hydrocarbon such as toluene, benzene or xylene.

Intermediate compounds of formula V may also themselves be used as pharmaceuticals, for example in the treatment or prevention of a condition characterised by stimulation of a $GABA_B$ receptor, particularly in de-esterified form, i.e. where R^5 has been replaced by hydrogen and any carboxylic ester group in R^3 and/or R^4 has been converted into a carboxyl group. Accordingly, the invention includes novel compounds of formula



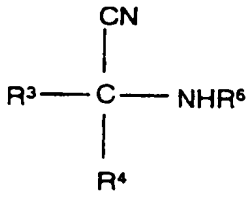
VA

where R^1 and R^2 are as hereinbefore defined, or salts or esters thereof.

Compounds of formula II are in some instances commercially available, e.g. (R) and (S) - phenyl glycinols. Compounds of formula II may be prepared by reduction of an aminocarboxylic acid of formula $R^3C(R^4)(NH_2)COOH$, where R^3 and R^4 are as hereinbefore defined in formula II, by reaction with borane dimethyl sulphide in the presence of a boron trifluoride complex such as boron trifluoride diethyl etherate. This reaction may be carried out using known procedures.

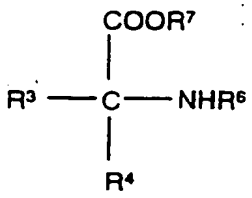
The compounds of formula II where R^3 is substituted by nitro may be prepared from an aminocarboxylic acid of formula $R^3C(R^4)(NH_2)COOH$, where R^3 is otherwise unsubstituted, by nitration to introduce a nitro group into R^3, converting the amino group in the product into a protected amino group, for example by reaction with di-tert-butyl dicarbonate to form a tert-butylcarbamate group, esterifying the carboxyl group in the protected product for example by conversion into a methyl ester, then reducing the ester group to $-CH_2OH$ by treatment with an appropriate reducing agent such as an alkali metal borohydride and finally removing the amino-protecting group by treatment with acid to re-form a free amino group. These reactions may be carried out using known procedures or minor modifications thereof.

Compounds of formula II may also be prepared by a Strecker synthesis in which an aldehyde or ketone of formula $R^3C(=O)R^4$, where R^3 and R^4 are as hereinbefore defined, is reacted with a compound of formula R^6NH_2, where R^6 is hydrogen or an alkyl group of 1 to 8 carbon atoms optionally substituted by a C_6 to C_{10} aryl group which is unsubstituted or substituted, for example by hydroxy or C_1 to C_4 alkoxy, and an alkali metal cyanide to give a compound of formula



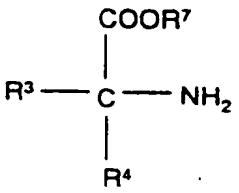
VI

where R^3, and R^4 and R^6 are as hereinbefore defined, reacting the compound of formula VI with an alcohol of formula R^7OH, where R^7 is an alkyl group of 1 to 10 carbon atoms, e.g. n-hexyl, 2-ethylhexyl, n-octyl or decyl, preferably C_1 to C_4 alkyl such as methyl, ethyl, isopropyl or n-butyl, especially methyl or ethyl, in the presence of an acid to form a compound of formula



VII

where R^3, R^4, R^6 and R^7 are as hereinbefore defined, removing R^6, when this is other than hydrogen, from the compound of formula VII using, for example, known procedures to give a compound of formula



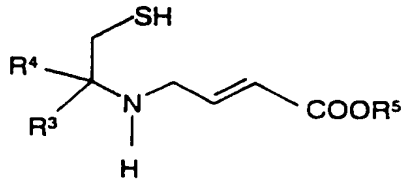
VIII

where R^3, R^4 and R^7 are as hereinbefore defined, for example, where R^6 is an optionally substituted benzyl group, by catalytic hydrogenation in the presence of an organic acid, e.g. acetic acid, to give a compound of formula VIII in the form of a salt thereof with the organic acid, reacting the compound of formula VIII with an amino-protecting agent such as tert-butyl dicarbonate to convert the amino group into a protected amino group, reducing the ester group $-COOR^7$ in the protected compound to $-CH_2OH$ by reaction with an appropriate reducing agent such as an alkali metal borohydride, and finally removing the protecting group to form a free amino group. This sequence of reactions may be carried out using known procedures, or minor modifications thereof. Where R^3 is substituted by a carboxylic ester group, the protected amino group formed should be a group such as a tert-butyl carbamate group which will permit the ester group $-COOR^7$ to be reduced to $-CH_2OH$ while leaving the ester group in R^3 and then be removable by a reaction, for example in a non-aqueous medium, which leaves the ester group in R^3.

In a modification of the Strecker synthesis hereinbefore described, the compound of formula VI may be subjected to acid hydrolysis, for example using conventional procedures, to convert the indicated cyano group to carboxyl and the resulting aminocarboxylic acid may be reduced to a compound of formula II by reaction with borane dimethyl sulphide in the presence of a boron trifluoride complex such as boron trifluoride diethyl etherate, for instance using known procedures.

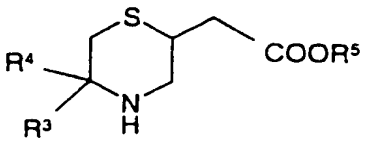
Compounds of formula III are commercially available or may be prepared by known procedures.

Compounds of formula I where X is carboxy and Y is sulphur may be prepared by reacting a compound of formula



IX

where R^3, R^4 and R^5 are as hereinbefore defined with an acid for example gaseous hydrogen chloride in ethanol or with a base, for example aqueous sodium hydrogen carbonate or a tertiary amine such as triethylamine, to give a compound of formula

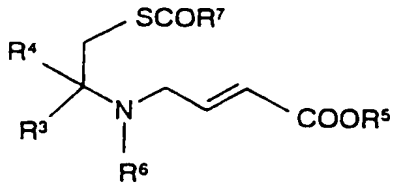


X

where R^3, R^4 and R^5 are as hereinbefore defined followed, where required, by one or more substitution reactions to change the nature of a substituent in R^3 and/or R^4 and/or by hydrolysis of an ester substituent in R^3 and/or R^4 to carboxyl and/or by hydrolysis of the ester group $-COOR^5$ to carboxyl.

The reaction of the compound of formula IX with acid may be carried out at a temperature from -20 to 80°C. The reaction of the compound of formula IX with a tertiary amine may conveniently be carried out in a protic solvent such as a mixture of methanol and water. The reaction with base may be carried out at -20 to 60°C.

Compounds of formula IX which are novel, may be prepared by reacting a compound of formula



XI

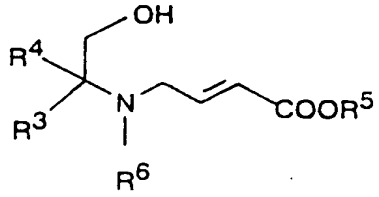
where R^3, R^4 and R^5 are as hereinbefore defined, R^6 is a N-H protecting group and R^7 is C_1 to C_8 alkyl, preferably C_1 to C_4 alkyl, especially methyl, with an acid to convert the $-SCOR^7$ group into -SH and, where the reaction to convert the $-SCOR^7$ group into -SH does not also convert R^6 into

hydrogen, subjecting the product of the reaction to a deprotection reaction to convert R^6 into hydrogen.

In formula XI, the protecting group R^6 is preferably an alkoxycarbonyl or aralkyloxycarbonyl group such as tert-butoxycarbonyl or benzyloxycarbonyl.

In the reaction of the compound of formula XI with acid, the acid may conveniently be hydrogen chloride gas in an alcohol, preferably ethanol, and the reaction may conveniently by carried out at -20 to 80°C. Where R^6 is a tert-butoxycarbonyl group, reaction with hydrogen chloride gas in an alcohol. in addition to converting -$SCOR^7$ into -SH, also converts R^6 into hydrogen. In this case, the compound of formula IX is generally not isolatable, being converted immediately into a compound of formula X. Where R^6 is other than tert-butoxycarbonyl, a subsequent reaction may be required to convert R^6 into hydrogen, for example using a conventional deprotection method for the protecting group R^6 concerned.

Compounds of formula XI which are novel, may be prepared by reacting a compound of formula

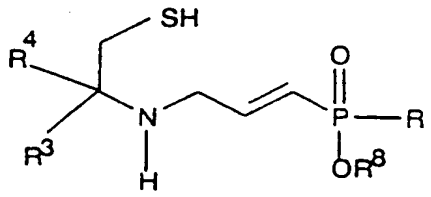


XII

where R^3, R^4, R^5 and R^6 are as hereinbefore defined. with a thioacid of formula R^7COSH where R^7 is as hereinbefore defined in the presence of a triarylphosphine, preferably triphenylphosphine, and a dialkylazodicarboxylate, preferably diethyl- or diisopropyl-azodicarboxylate, in an aprotic solvent such as tetrahydrofuran (THF). The reaction may be carried out at -20 to 50°C.

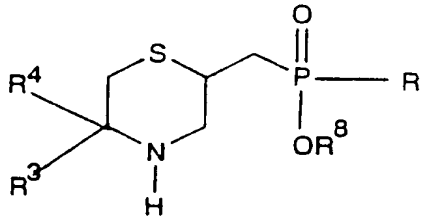
Compounds of formula XII, which are novel, may be prepared by reacting a compound of formula V with a reagent known to introduce the desired protecting group R^6, for example using known procedures. Where R^6 is an alkoxycarbonyl or aralkoxycarbonyl group, the compound of formula V may be reacted with an alkyl or aralkyl dicarbonate such as di-tert-butyl dicarbonate or with an alkoxycarbonyl or aralkoxycarbonyl halide such as benzyl chloroformate, for example using known procedures such as reaction with di-tert-butyl dicarbonate in THF at 20-70°C.

Compounds of formula I where X is -PO(OH)-R and Y is sulfur may be prepared by reacting a compound of formula



XIII

where R, R^3 and R^4 are as hereinbefore defined and R^8 is C_1 to C_8 alkyl, preferably C_1 to C_4 alkyl, especially ethyl, with a base, for example a tertiary amine such as triethylamine, to give a compound of formula



XIV

where R, R^3, R^4 and R^8 are as hereinbefore defined in formula XIII, followed, where required, by one or more substitution reactions to change the nature of a substituent in R^3 and/or R^4, and/or by hydrolysis of an ester substituent in R^3 and/or R^4 to carboxyl and/or by conversion of the ester group $-OR^8$ to -OH.

The reaction of the compound of formula XIII with a base may conveniently be carried out in a protic solvent such as a mixture of methanol and water. The reaction may be carried out at -20 to 60°C.

Compounds of formula I in which R^1 and/or R^2 contains a cyano substituent on an aryl or heteroaryl ring may be prepared by reacting an alkali metal cyanide with a compound of formula I, IV, X or XIV where R^1 or R^3 and/or R^2 or R^4 respectively contains a halogen substituent on an aryl or heteroaryl ring. Compounds of formula I, IV, X or XIV where R^1 or R^3 and/or R^2 or R^4 respectively contains an amino group on an aryl or heteroaryl ring, may be prepared by reduction of a compound of formula I, IV, X or XIV in which R^1 or R^3 and/or R^2 or R^4 respectively contains a nitro group on an aryl or heteroaryl ring. All of these reactions can be effected using known procedures.

Compounds of formula I in which R^1 and/or R^2 contains an esterified carboxyl substituent can also be prepared from other compounds of formula I, IV, X or XIV. For example, they may be prepared by reacting a compound of formula I, IV, X or XIV in which R^1 or R^3 and/or R^2 or R^4 respectively contains a halogen substituent on an aryl or heteroaryl ring with carbon monoxide and an alcohol in the presence of a palladium complex as catalyst, using known procedures.

Compounds of formula I in which R^1 and/or R^2 contains a carboxyl substituent may be prepared by hydrolysis of a compound of formula I, IV, X or XIV in which R^1 or R^3 and/or R^2 or R^4 respectively contains an esterified carboxyl substituent using conventional hydrolysis procedures.

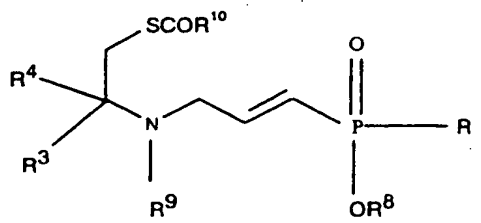
Where, in a compound of formula IV or X, R^3 or R^4 contains an esterified carboxyl group, this may be hydrolysed to a free carboxyl group using conventional methods. Where R^3 or R^4 in the compound of formula IV or X contains a nitro group on an aryl or heteroaryl ring, this group may be converted in turn to amino by reduction, to halo by diazotisation of amino followed by reaction with an alkali metal halide, to cyano by reaction of halo with an alkali metal cyanide and thence to carboxyl by hydrolysis of cyano, these reactions conveniently being carried out using known procedures.

The conversion of the ester group $-COOR^5$ in a compound of formula IV or V into carboxyl can be effected by conventional procedures for the hydrolysis of carboxylic esters, for example by the reaction used to hydrolyse a carboxylic ester group in R^3 or R^4.

The conversion of the ester group $-OR^8$ in a compound of formula XIV into -OH can be effected by treatment with a suitable basic or acidic agent, such as an alkali metal hydroxide, for example sodium hydroxide or lithium hydroxide, an alkali metal halide, especially an alkali metal bromide or iodide, such as lithium bromide or sodium iodide, thiourea, an alkali metal thiophenolate, such as sodium thiophenolate, or a protonic acid or a Lewis acid, such as a mineral acid, for example hydrochloric acid, or a tri-lower alkyl-halosilane, for example trimethylchlorosilane. The replacement reaction can be effected in the absence or presence of a solvent and, if necessary, with heating or with cooling in a closed vessel and/or under an inert gas atmosphere.

The conversion of -OR^8 in a compound of formula III into -OH can also be carried out by treatment with an acid under hydrolytic conditions, especially with a mineral acid, such as a hydrohalic acid, for example hydrochloric acid, which is used in dilute or concentrated aqueous form, or by treatment with an organic silyl halide, such as trimethylsilyl iodide or bromide, and, if necessary, by subsequent hydrolysis. The reaction is preferably carried out at elevated temperature, for example by maintaining the reaction mixture at reflux temperature, and, where appropriate, using an organic diluent in a closed vessel and/or under an inert gas atmosphere.

Compounds of formula XIII, which are novel, may be prepared by reacting a compound of formula



XV

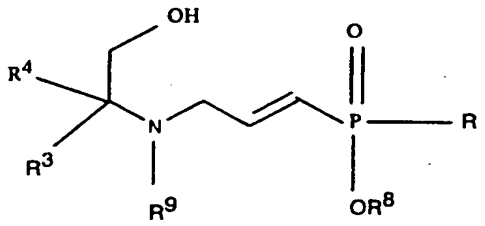
where R, R^3, R^4 and R^8 are as hereinbefore defined in formula XIII, R^9 is a N-H protecting group and R^{10} is C_1 to C_8 alkyl, preferably C_1 to C_4 alkyl, especially methyl, with an acid to convert the -$SCOR^{10}$ group into -SH and, where the reaction to convert the -$SCOR^{10}$ group into -SH does not also convert R^9 into hydrogen, subjecting the product of the reaction to a deprotection reaction to convert R^9 into hydrogen.

In formula XV, the protecting group R^9 is preferably an alkoxycarbonyl or aralkyloxycarbonyl group such as tert-butoxycarbonyl or benzyloxycarbonyl.

In the reaction of the compound of formula XV with acid, the acid may conveniently be hydrogen chloride gas in an alcohol, preferably ethanol, and the reaction may conveniently be carried out at -20 to 80°C. Where R^9 is a tert-butoxycarbonyl group, reaction with hydrogen chloride gas in an alcohol, in addition to converting -$SCOR^{10}$ into -SH, also converts R^9 into hydrogen. Where R^9 is other than tert-butoxycarbonyl, a subsequent

reaction may be required to convert R^9 into hydrogen, for example using a conventional deprotection method for the protecting group R^9 concerned.

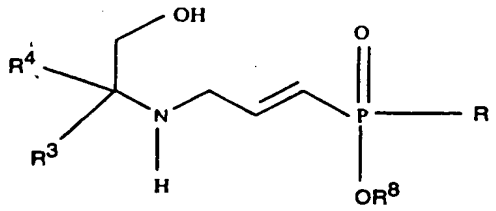
Compounds of formula XV, which are novel, may be prepared by reacting a compound of formula



XVI

where R, R^3, R^4, R^8 and R^9 are as hereinbefore defined in formula XV, with a thioacid of formula $R^{10}COSH$ where R^{10} is as hereinbefore defined in the presence of a triarylphosphine, preferably triphenylphosphine, and a dialkylazodicarboxylate, preferably diethyl- or diisopropyl- azodicarboxylate, in an aprotic solvent such as tetrahydrofuran (THF). The reaction may be carried out at -20 to 50°C.

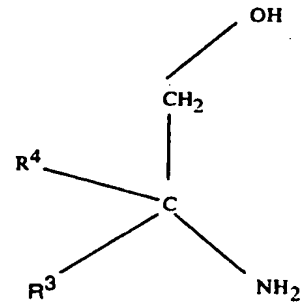
Compounds of formula XVI, which are novel, may be prepared by reacting a compound of formula



XVIA

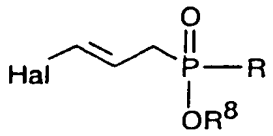
where R^3, R^4, R^8 and R are as hereinbefore defined in formula VIII, with a reagent known to introduce the desired protecting group R^9, for example using known procedures. Where R^9 is an alkoxycarbonyl or aralkoxycarbonyl group, the compound of formula XVIA may be reacted with an alkyl or aralkyl dicarbonate such as di-tert-butyl dicarbonate or with an alkoxycarbonyl or aralkoxycarbonyl halide such as benzyl chloroformate, for example using known procedures such as reaction with di-tert-butyl dicarbonate in THF at 20-70°C.

Compounds of formula XVIA may be prepared by reacting a compound of formula



XVII

where R^3 and R^4 are as hereinbefore defined in formula XIII, with a compound of formula



XVIII

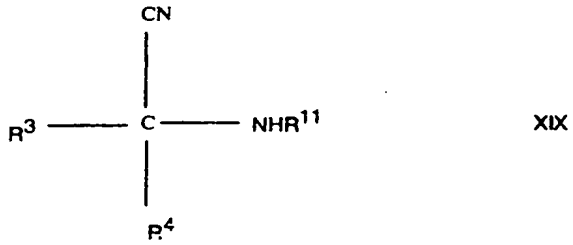
where R and R^8 are as hereinbefore defined and Hal is halogen, e.g. chlorine or bromine, in the presence of a weak base, for example a hindered amine such as 1,8-diazabicylo[5.4.0]undec-7-ene (DBU), in a solvent, preferably a hydrocarbon such as benzene, toluene or xylene, at a temperature of 70 to 110°C.

Compounds of formula XVII are in some instances commercially available, e.g. (R) - and (S) - phenyl glycinols. Compounds of formula XVII may be prepared by reduction of an aminocarboxylic acid of formula $R^3C(R^4)(NH_2)COOH$, where R^3 and R^4 are as hereinbefore defined in formula XIII, by reaction with borane dimethyl sulphide in the presence of a boron trifluoride complex such as boron trifluoride diethyl etherate. This reaction may be carried out using known procedures.

The compounds of formula XVII where R^3 is substituted by nitro may be prepared from an aminocarboxylic acid of formula $R^3C(R^4)(NH_2)COOH$ where R^3 is otherwise unsubstituted by nitration to introduce a nitro group into R^3, converting the amino group in the product into a protected amino group, for example by reaction with di-tert-butyl dicarbonate to form a tert-butylcarbamate group, esterifying the carboxyl group in the protected product for example by conversion into a methyl ester, then reducing the ester

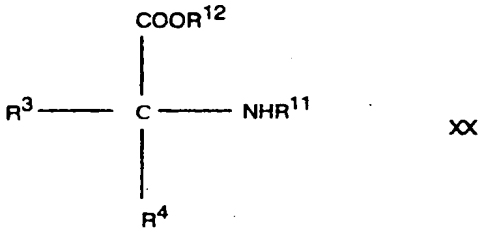
group to -CH_2OH by treatment with an appropriate reducing agent such as an alkali metal borohydride and finally removing the amino-protecting group by treatment with acid to re-form a free amino group. These reactions may be carried out using known procedures or minor modifications thereof.

Compounds of formula XVII may also be prepared by a Strecker synthesis in which an aldehyde or ketone of formula $R^3C(=O)R^4$, where R^3 and R^4 are as hereinbefore defined in formula XIII, is reacted with a compound of formula $R^{11}NH_2$, where R^{11} is hydrogen or an alkyl group of 1 to 8 carbon atoms optionally substituted by a C_6 to C_{10} aryl group which is unsubstituted or substituted, for example by hydroxy or C_1 to C_4 alkoxy, and an alkali metal cyanide to give a compound of formula



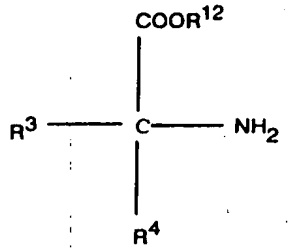
XIX

where R^3, R^4 and R^{11} are as hereinbefore defined, reacting the compound of formula XIX with an alcohol of formula $R^{12}OH$, where R^{12} is an alkyl group of 1 to 10 carbon atoms, e.g. n-hexyl, 2-ethylhexyl, n-octyl or decyl, preferably $C_1$to C_4 alkyl such as methyl, ethyl, isopropyl or n-butyl, especially methyl or ethyl, in the presence of an acid to form a compound of formula



XX

where R^3, R^4, R^{11} and R^{12} are as hereinbefore defined, removing R^{11}, when this is other than hydrogen, from the compound of formula XX using, for example, known procedures to give a compound of formula

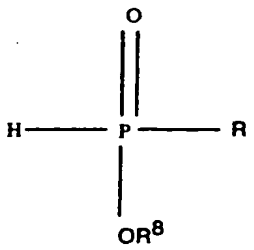


XXI

where R^3, R^4 and R^{12} are as hereinbefore defined, for example, where R^{11} is an optionally substituted benzyl group, by catalytic hydrogenation in the presence of an organic acid, e.g. acetic acid, to give a compound of formula XXI in the form of a salt thereof with the organic acid, reacting the compound of formula XXI with an amino-protecting agent such as tert-butyl dicarbonate to convert the amino group into a protected amino group, reducing the ester group $-COOR^{12}$ in the protected compound to $-CH_2OH$ by reaction with an appropriate reducing agent such as an alkali metal borohydride, and finally removing the protecting group to form a free amino group. This sequence of reactions may be carried out using known procedures, or minor modifications thereof. Where R^3 is substituted by a carboxylic ester group, the protected amino group formed should be a group such as a tert-butyl carbamate group which will permit the ester group $-COOR^{12}$ to be reduced to $-CH_2OH$ while leaving the ester group in R^3 and then be removable by a reaction, for example in a non-aqueous medium, which leaves the ester group in R^3.

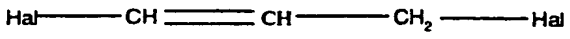
In a modification of the Strecker synthesis hereinbefore described, the compound of formula XIX may be subjected to acid hydrolysis, for example using conventional procedures, to convert the indicated cyano group to carboxyl and the resulting aminocarboxylic acid may be reduced to a compound of formula XVII by reaction with borane dimethyl sulphide in the presence of a boron trifluoride complex such as boron trifluoride diethyl etherate, for instance using known procedures.

Compounds of formula XVIII may be prepared by reacting a compound of formula



XXII

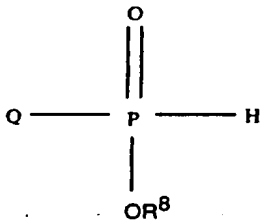
with a compound of formula



XXIII

where R, R^8 and Hal are as hereinbefore defined, in the presence of a silylating agent such as a bis(trialkylsilyl) derivative of an amide, which agent undergoes reaction with the compound of formula XXII to form a P(III) silyl compound which then reacts with the compound of formula XXIII. The reaction may be carried out at a temperature from 0 to 50°C; it is preferably carried out in a solvent, for example a hydrocarbon such as toluene or a halohydrocarbon such as dichloromethane.

Esters of formula XXII may be prepared by reacting a protected phosphinate ester of formula

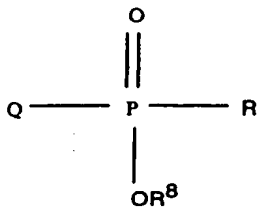


XXIV

where R^8 is as hereinbefore defined and Q is a P-H-protecting group, with a compound of formula

RZ XXV

where R is as hereinbefore defined and Z is a leaving moiety, to give a compound of formula



XXVI

and then replacing the protecting group Q in the compound of formula XXVI by hydrogen. The leaving moiety Z may be, for example, a halogen atom or an organic sulphonate group. Preferably Z is chlorine, bromine, iodine, or a methanesulphonate, trifluoromethanesulphonate or p-toluenesulphonate group. The reaction between the compounds of formulae XXIV and XXV and the deprotection reaction on the compound of formula XXVI may be carried out using known procedures, for example as described in EP 0569333.

Protected phosphinate esters of formula XXIV may be prepared by known methods, for example as described in US 4 933 478. Compounds of formula XXV are either commercially available or may be prepared by known procedures.

Compounds of formula XXIII are dihaloalkenes which are either commercially available or may be prepared using known methods.

Compounds of the invention obtained as salts can be converted into the free compounds in a manner known per se, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or metal hydrogen carbonate, or ammonia, or another of the salt-forming bases mentioned hereinbefore, or with an acid, such as a mineral acid, for example with hydrochloric acid, or another of the salt-forming acids mentioned hereinbefore.

Salts of the invention can be converted into different salts of the invention in a manner known per se; for example, acid addition salts can be converted by treatment with a suitable metal salt, such as a sodium, barium or silver salt, of another acid in a suitable solvent in which an inorganic salt being formed is insoluble and is thus excluded from the reaction equilibrium, and base salts can be converted by freeing the free acid and converting into a salt again.

The compounds of formula I, including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallisation.

Owing to the close relationship between the novel compounds in free form and in the form of their salts, hereinbefore and hereinafter the free compounds and their salts are also optionally to be understood as being the corresponding salts and free compounds, respectively, where appropriate and where the context so allows.

For compounds of formula I, and intermediates in the preparation thereof, diastereoisomeric mixtures and mixtures of racemates can be separated in known manner into the pure diastereoisomers and racemates, respectively, on the basis of the physicochemical differences between their constituents, for example by chromatography and/or fractional crystallisation.

Resulting racemates can also be resolved into the optical antipodes by known methods, for example by recrystallisation from an optically active solvent, with the aid of microorganisms or by reaction of the resulting diastereoisomeric mixture or racemate with an optically active auxiliary compound, for example according to the acidic, basic or functionally modifiable groups contained in compounds of formula I, with an optically active acid, base or an optically active alcohol, into mixtures of diastereoisomeric salts or functional derivatives, such as esters, and separation of the same into the diastereoisomers from which the desired enantiomer can be freed in customary manner. Suitable bases, acids and alcohols for the purpose are, for example, optically active alkaloid bases, such as strychnine, cinchonine or brucine, or D- or L-(1-phenyl)ethylamine, 3-pipecoline, ephedrine, amphetamine and similar bases that can be obtained by synthesis, optically active carboxylic or sulfonic acids, such as quinic acid or D- or L- tartaric acid, D- or L-di-o-toluoyltartaric acid, D- or L-malic acid, D- or L- mandelic acid, or D- or L-camphorsulfonic acid, or optically active alcohols, such as borneol or D- or L- (1-phenyl)ethanol.

Compounds of formula I may be isotopically labelled, particularly with ^{11}C, ^{14}C, ^{2}H, ^{3}H or ^{125}I for use in diagnostics.

The compounds of formula I may be used, for example, in the form of pharmaceutical compositions that comprise a therapeutically effective amount of the active ingredient, where appropriate together with pharmaceutically acceptable carriers that are suitable for enteral, for example oral, or parenteral administration, which carriers may be solid or liquid and organic or inorganic. For example, tablets or gelatin capsules are used that contain the active ingredient together with diluents, for example lactose, dextrose, saccharose, mannitol, sorbitol, cellulose and/or lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Tablets may also contain binders, for example magnesium aluminium silicate, starches, such as corn, wheat, rice or arrowroot starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, for example sodium alginate, and/or effervescent mixtures, or absorbents, colourings, flavourings and sweeteners. The compounds of formula I can also be used in the form of parenterally administrable compositions or in the form of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions which, for example in the case of lyophilised compositions that comprise the active ingredient on its own or together with a carrier, for example mannitol, can be prepared before use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical compositions which, if desired, may comprise other pharmacologically active substances, may be prepared in a manner known per se, for example by conventional mixing, granulating, confectioning, dissolving or lyophilising processes, and may comprise approximately from 0.1% to 100%, especially from approximately 1% to approximately 50%, and, in the case of lyophilisates, up to approximately 100%, active ingredient.

The invention relates also to the use of the compounds of formula I, or salts or esters thereof, preferably in the form of pharmaceutical compositions.

The dose may depend on various factors, such as the mode of administration, species, age and/or individual condition. The doses to be administered daily may, in the case of oral administration, be from approximately 1 to approximately 50mg/kg, especially from 5 to approximately 25mg/kg, and, in the case of warm-blooded animals having a body weight of approximately 70 kg, preferably from

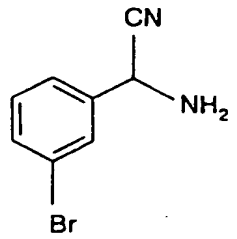
approximately 70 mg to approximately 3500 mg, especially from approximately 350 to approximately 1750 mg, expediently divided into from 2 to 6, for example 3 or 4, single doses.

The invention accordingly includes a method of treating or preventing a condition in warm-blooded mammals, particularly humans, characterised by stimulation of a $GABA_B$ receptor which comprises administering to the warm blooded mammal a compound of formula I or VA, or a pharmaceutically acceptable salt or ester thereof.

The invention is illustrated by the following Examples.

Compound C used in the Examples is prepared as follows:

Sodium cyanide (4.9g, 0.1M) and ammonium chloride (5.88g, 0.11M) are stirred in water (20ml) at room temperature. A solution of 3-bromobenzaldehyde (18.5g, 0.1M) in methanol (30ml) is added dropwise over one minute. Aqueous ammonia solution (10ml, specific gravity 0.88) is added and the reaction mixture is stirred for 3 hours at room temperature. Ethyl acetate is added and the organic phase separated, dried over magnesium sulphate, filtered and evaporated. The residue is dissolved in ethyl acetate and repeatedly extracted with 2N hydrochloric acid. The combined aqueous layers are adjusted to pH9 using aqueous ammonia solution and re-extracted repeatedly with ethyl acetate. The combined organic layers are dried over magnesium sulphate, filtered and evaporated under reduced pressure to afford an orange oil which is purified by flash chromatography on silica using hexane:ethyl acetate (1:1) as eluant to afford Compound A.

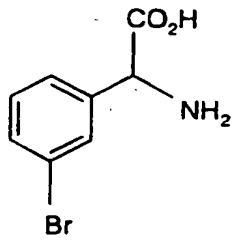


Compound A

^{13}C nmr (100 MHz; $CDCl_3$): δ (ppm) 46.6 (d), 120.4 (S), 122.9 (S), 125.2 (d), 129.7 (d), 130.5 (d), 132.1 (d), 138.3 (S).

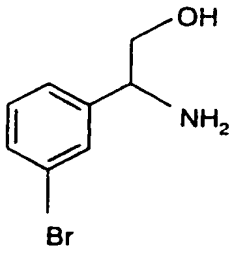
A mixture of Compound A (10.5g, 49.8 mM) in 6M hydrochloric acid (200ml) is heated under reflux for 68 hours. The supernatant is decanted off, cooled to room temperature and adjusted to pH7

using aqueous ammonia solution. The precipitated product is collected by filtration, washed with water and dried. Trituration with ethyl acetate followed by drying affords Compound B as a brown solid. m.p. 201-204°C (dec).



Compound B

^{13}C nmr (100 MHz; CD_3OD) : δ (ppm) 56.9 (d), 124.0 (S), 128.1 (d), 132.2 (2 x d), 134.0 (d), 136.0 (S), 170.1 (S).

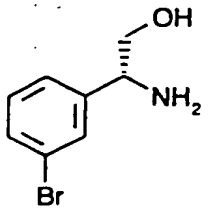


Compound C

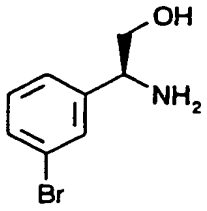
Boron trifluoride ethyl etherate (75.0ml, 0.61M) is added dropwise to suspension of Compound B (70.2g, 0.31M) in THF (350ml) over 20 minutes. The mixture is heated under reflux for 2 hours, then borane dimethyl sulphide complex (57.9ml, 0.61M) is added dropwise over 1.5 hours whilst maintaining the mixture at reflux. The mixture is heated under reflux for a further 3 hours and then stood for 18 hours at room temperature. A 1:1 mixture of water and THF (350ml) is added followed by 5M sodium hydroxide solution (350ml). The reaction mixture is heated under reflux for 5 hours then cooled to room temperature. The two layers are separated and the aqueous layer extracted with ethyl acetate. The combined organic phases are washed with brine, dried over magnesium sulphate, filtered and evaporated under reduced pressure to afford a brown oil. This residue is triturated with diethyl ether/hexane then recrystallised from ethyl acetate to afford Compound C m.p. 74-76°C.

Found C, 44.40; H, 4.67; N, 6.35%.

$C_8H_{10}Br$ NO requires C, 44.46; H, 4.67; N, 6.48%.



(R)-enantiomer



(S)-enantiomer

Compound C

Racemic Compound C can be resolved into the two enantiomers using fractional crystallization of the diasteromeric salts with (D)-(-)-tartaric acid in water to obtain the (R)-(-)-enantiomer of Compound C.

m.p. 69-71°C.

$[\alpha]_D$ = -35.6° (c = 0.5, $CHCl_3$)

enantiomeric excess: 99.4% as determined by HPLC on chiral columns

Chromasil CHI-I 100-5 25 × 0.46 cm, eluted with 3% ethanol in heptane containing 0.1% trifluoroacetic acid; t_R = 12.67 min.

Found C, 44.48; H, 4.66; N, 6.40

$C_8H_{10}BrNO$ requires C, 44.46; H,4.67; N, 6.48%.

and with (L)-(+)-tartaric acid to obtain the (S)-(+)-enantiomer of Compound C

m.p. 69-70°C.

$[\alpha]_D$ = +34.7° (c = 0.5, $CHCl_3$)

enantiomeric excess: 99.6% as determined by HPLC on chiral columns

Chromasil CHI-I 100-5 25 × 0.46 cm, eluted with 3% ethanol in heptane containing 0.1% trifluoroacetic acid; t_R = 14.34 min.

Found C, 44.48; H, 4.67; N, 6.37

$C_8H_{10}BrNO$ requires C, 44.46; H,4.67; N, 6.48%.

Compound D used in the Examples is prepared as follows:

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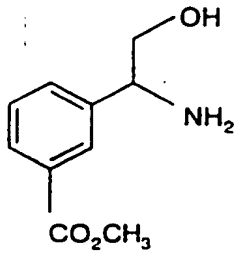
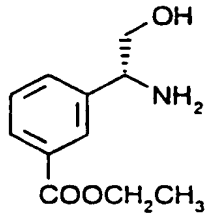


Compound D

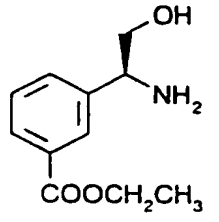
A mixture of Compound C (15.0g, 69.4mM) and bis(triphenylphosphine) palladium (II) chloride (4.0g, 5.70mM) in methanol (100ml) and triethylamine (25ml) is degassed by sparging with argon for 5 minutes. The mixture is saturated with carbon monoxide and then pressurised to 30 psi in a pressure vessel. The mixture is slowly heated to 100°C whilst maintaining the pressure below 50 psi for 5 hours. The mixture is cooled to room temperature, filtered and evaporated. The residue is triturated with ethyl acetate and the filtrate evaporated. The residue is purified by flash chromatography on silica using a gradient from 10% to 20% methanol in chloroform as eluant to afford Compound D.

^{13}C nmr (100MHz; CD_3OD): δ (ppm) 52.6 (q), 58.3 (d), 68.1 (t), 129.0 (d), 129.5 (d), 129.7 (d), 131.5 (s), 132.9 (d), 143.6 (s), 168.4 (s).

The (R)-(-)- and the (S)-(+)-enantiomer of Compound D used in the Examples are prepared as follows:



(R)-enantiomer



(S)-enantiomer

Compound D

Starting from (R)-enantiomer of Compound C by reaction with carbon monoxide in ethanol using bis(triphenylphosphine) palladium (II) chloride as catalyst the (R)-enantiomer of Compound D ethylester is obtained as an oil.

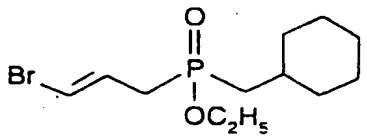
$[\alpha]_D$ = -30.6° (c = 0.25, $CHCl_3$).

Starting from the (S)-enantiomer of Compound C the (S)-enantiomer of Compound D ethylester is obtained.

$[\alpha]_D$ = +29.2° (c = 0.25, $CHCl_3$).

Compound F used in the Examples is prepared as follows:

Bis(trimethylsilyl)acetamide (28.51ml) is added dropwise to a solution of 18.22g of ethyl cyclohexylmethylphosphinate, prepared as described in EP 0569333, in 100ml of dry CH_2Cl_2 under argon. The solution is stirred at room temperature for 1 hour, then trimethyl phosphate (13.42ml) is added, followed by 1,3-dibromopropene (mixture of cis/trans isomers) (9.57ml). After stirring the solution at room temperature for 18 hours, it is poured into saturated aqueous $NaHCO_3$ solution (100ml) and stirred for 10 minutes. The product is extracted with CH_2Cl_2 (3 x 50 ml) and the combined organic extracts are washed with brine, then dried with $MgSO_4$ and filtered. The filtrate is evaporated under reduced pressure, then excess trimethyl phosphate is removed by evaporation at 80°C at 0.45mm Hg. The residue is purified by flash chromatography (silica gel, ethyl acetate) to yield Compound E as a mixture of cis and trans isomers.

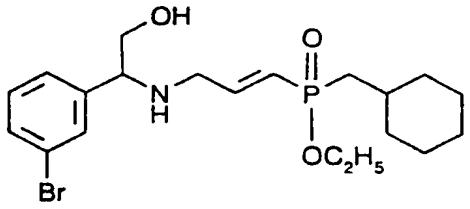


Compound E

^{31}P nmr (162MHz, $CDCl_3$): δ (ppm) 51.1 and 52.2.

A mixture of Compound C (2.2g, 10.2mM) and Compound E (3.15g, 10.2mM) in dry toluene (20ml) is heated to 75°C under argon. A solution of 1,8-diazabicyclo [5.4.0] undec-7-ene (1.9g, 12.2mM) in dry toluene (10ml) is added dropwise over 2 hours. The mixture is cooled to room temperature and allowed to stand for 18 hours. The mixture is

filtered and the filtrate evaporated under reduced pressure to afford a yellow oil which is purified by flash chromatography on silica using 10% methanol in ethyl acetate as eluant to give Compound F as a mixture of diastereomers at phosphorus.



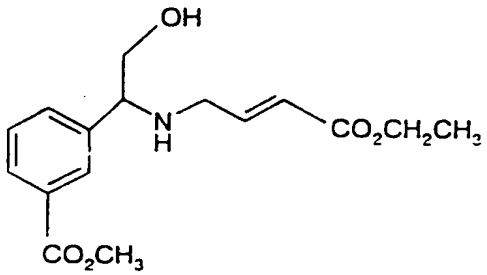
Compound F

Found: C, 53.37; H, 7.33; N, 2.94%.

$C_{20}H_{31}Br\ NO_3P.\ 0.5H_2O$ requires C, 52.99; H, 7.11; N, 3.09%.

^{31}P nmr (162MHz; $CDCl_3$): δ (ppm) 43.25 and 43.31.

Example 1



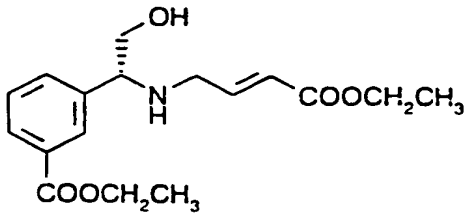
Compound 1

Diisopropylethylamine (2.0ml, 11.61mM) is added to a solution of Compound D (1.50g, 7.80mM) and ethyl 4-bromocrotonate (1.28ml. 9.32mM) in dichloromethane (20ml). The resulting mixture is stirred for 8 days at room temperature. Ethyl acetate is added and the mixture is stirred for a further 0.5 hours. The mixture is filtered to remove the precipitated diisopropylethyl amine hydrobromide and the filtrate is evaporated under reduced pressure to afford a yellow oil which is purified by flash chromatography on silica using a gradient from 60% to 80% ethyl acetate in hexane as eluant to afford Compound 1.

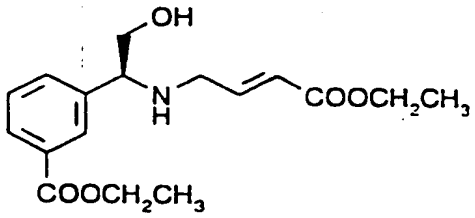
Found C, 61.74; H, 6.92; N, 4.54%.

$C_{16}H_{21}NO_5.0.25\ H_2O$ requires C, 61.62; H, 6.95; N, 4.49%.

mass spec. (CI, NH_3): $(m + 1)^+$ m/z = 308.



(R)-enantiomer



(S)-enantiomer

Compound 1

By condensation of the (R)-enantiomer of Compound D ethylester with ethyl 4-bromocrotonate in dichloromethane using diisopropylethylamine the (R)-enantiomer of Compound 1 diethylester is obtained.

$C_{17}H_{23}NO_5$

mass spec. (CI, NH_3): $(m + 1)^+$ m/z = 322

By condensation of the (S)-enantiomer of Compound D ethylester with ethyl 4-bromocrotonate in dichloromethane using diisopropylethylamine the (S)-enantiomer of Compound 1 diethylester is obtained.

$C_{17}H_{23}NO_5$

mass spec. (CI. NH_3): $(m + 1)^+$ m/z = 322

Example 2

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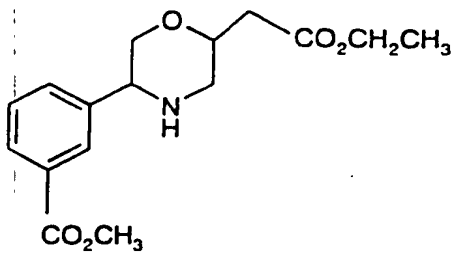


Compound 2 [trans]
Compound 3 [cis]

A suspension of sodium hydride (21mg, 0.88 mM) in toluene (1ml) is added portionwise to a cooled (0°C) solution of Compound 1 (210mg, 0.68mM) in dry toluene (2.5ml). The resulting mixture is stirred for 1 hour at 0°C and then warmed to room temperature and stirred for a further 18 hours. The reaction mixture is partitioned between ethyl acetate and saturated aqueous ammonium chloride solution. The aqueous phase is extracted with ethyl acetate and the combined organic layers are dried over magnesium sulphate, filtered and evaporated under reduced pressure to afford a yellow oil which is purified by flash chromatography on silica using a gradient from 60% to 80% ethyl acetate in hexane as eluant to afford trans -2, 5-disubstituted morpholine Compound 2 and cis-2, 5-disubstituted morpholine Compound 3.

Compound 2:

mass spec. (Cl, NH_3); $(m+1)^+$ m/z = 308.

^{13}C(125.8MHz; $CDCl_3$) δ (ppm)

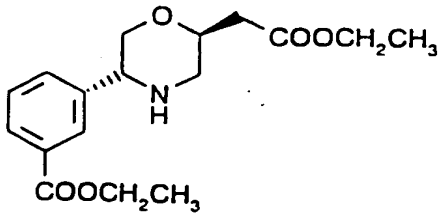
14.57 (q), 39.24 (t), 51.37 (t), 52.51 (q), 59.80 (d), 61.04 (t), 73.16 (d), 73.92 (t), 128.65 (d), 128.99 (d), 129.45 (d), 130.83 (s), 132.17 (d), 140.90 (s), 167.26 (s), 171.12 (s).

Compound 3:

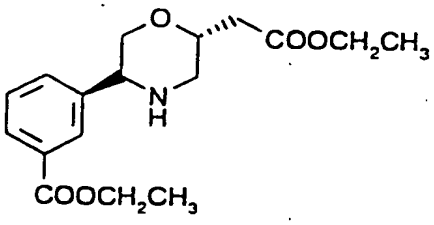
mass spec. (Cl, NH_3): $(m+1)^+$ m/z = 308.

^{13}C (125.8 MHz; $CDCl_3$) δ (ppm)

14.59 (q), 36.46 (t), 47.73 (t), 52.55 (q), 58.59 (d), 60.96 (t), 68.29 (t), 70.78 (d), 128.91 (d), 128.97 (d), 129.20 (d), 130.80 (s), 132.48 (d), 141.64 (s), 167.40 (s), 171.76 (s).

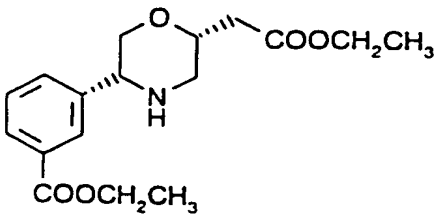


trans-(2S, 5R)-enantiomer

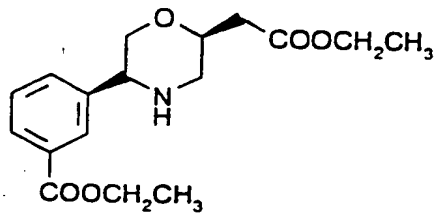


trans-(2R, 5S)-enantiomer

Compound 2 [trans]



cis-(2R, 5R)-enantiomer



cis-(2S, 5S)-enantiomer

Compound 3 [cis]

Cyclization of the (R)-enantiomer of Compound 1 diethylester by sodium hydride in toluene affords trans-(2S,5R)-2,5-disubstituted morpholine Compound 2 diethylester and cis-(2R,5R)-2,5-disubstituted morpholine Compound 3 diethylester.

(2S,5R)-Compound 2 diethylester:

$[\alpha]_D$ = -44.8° (c = 1, $CHCl_3$).

$C_{17}H_{23}NO_5$

mass spec. (CI, NH_3): $(m + 1)^+$ m/z = 322

(2R,5R)-Compound 3 diethylester:

$[\alpha]_D$ = -20.9° (c = 1, $CHCl_3$).

$C_{17}H_{23}NO_5$

mass spec. (CI, NH_3): $(m + 1)^+$ m/z = 322.

Equally base catalyzed cyclization of the (S)-enantiomer of Compound 1 diestylester in toluene affords trans-(2R,5S)-2,5-disubstituted morpholine Compound 2 diethylester and cis-(2S,5S)-2,5-disubstituted morpholine Compound 3 diethylester.

(2R,5S)-Compound 2 diethylester.

$[\alpha]_D$ = +43.8° (c = 1, $CHCl_3$).

$C_{17}H_{23}NO_5$

mass spec. (CI, NH_3): $(m + 1)^+$ m/z = 322

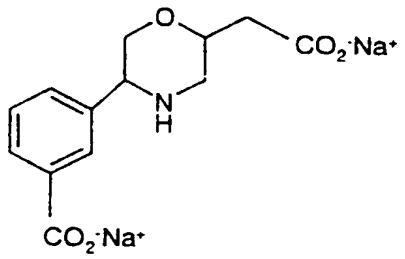
(2S,5S)-Compound 3 diethylester:

$[\alpha]_D$ = +16.3° (c = 1, $CHCl_3$).

$C_{17}H_{23}NO_5$

mass spec. (CI, NH_3): $(m + 1)^+$ m/z = 322.

Example 3



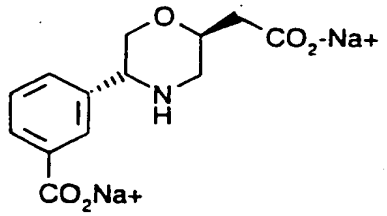
Compound 4

A solution of Compound 2 (49mg, 0.16mM) in a mixture of THF (2ml) and 6N hydrochloric acid (2ml) is heated at 80°C for 4 hours. The mixture is cooled to room temperature and allowed to stand at room temperature for a further 18 hours. The mixture is evaporated to dryness under reduced pressure and the residue is purified by ion exchange chromatography on Dowex 50 WX 2-200 resin (H^+ form) using methanol : 2% sodium hydroxide solution (1:1) to elute the product. The resulting product is further purified by gel filtration on a BIO-GEL P2 column using water as eluant to afford the trans - 2, 5- disubstituted morpholine racemic Compound 4.

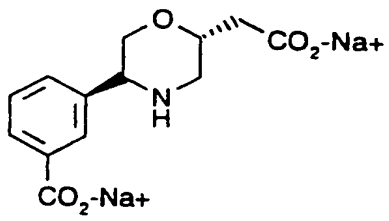
Found C, 46.35; H, 4.70; N, 3.79%

$C_{13}H_{13}NO_5$. 2Na. 1.5H_2O requires C, 46.44; H, 4.80; N,4.17%.

^{13}C nmr (125.8 MHz; D_2O) δ (ppm) 41.88 (t), 49.94 (t), 58.71 (d) 72.16 (t), 74.17 (d), 127.76 (d), 128.84 (d), 129.08 (d), 129.98 (d), 137.20 (s), 138.80 (s), 175.71 (s), 179.40 (s).

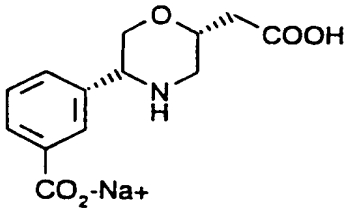


trans-(2S, 5R)-enantiomer

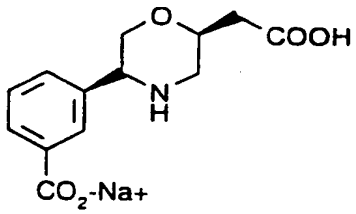


trans-(2R, 5S)-enantiomer

Compound 4 [trans]



cis-(2R, 5R)-enantiomer



cis-(2S, 5S)-enantiomer

Compound 4a [cis]

Hydrolysis of the trans-(2S,5R)-enantiomer of Compound 2 diethylester using a mixture of 6N hydrochloric acid and THF at 80°C for 18 hours, evaporation and purification by ion exchange chromatography on Dowex 50 WX2-200 resin (H+ form) using methanol : 2% sodium hydroxide solution (1:1) affords the disodium salt of trans-(2S.5R)-2.5-disubstituted morpholine Compound 4.

$[\alpha]_D$ = -6.8° (c = 1, H_2O).

Found C, 46.42: H, 5.01; N, 4.01%.

$C_{13}H_{13}NNa_2O_5.1.5\ H_2O$ requires C, 46.44; H, 4.80; N, 4.17%.

Hydrolysis of the cis-(2R,5R)-enantiomer of Compound 3 diethylester affords the monosodium salt of cis-(2R,5R)-2,5-disubstituted morpholine Compound 4a.

$[\alpha]_D$ = +9.2° (c = 0.184, H_2O).

Found C, 44.19; H, 4.75; N, 3.58%.

$C_{13}H_{14}NNaO_5$.1.6 NaOH requires C, 44.45; H, 4.48; N, 3.98%.

Hydrolysis of the trans-(2R,5S)-enantiomer of Compound 2 diethylester affords the disodium salt of trans-(2R,5S)-2,5-disubstituted morpholine Compound 4.

$[\alpha]_D$ = +5.4° (c = 1, H_2O).

Found C, 47.55; H, 5.09; N, 4.01%.

$C_{13}H_{13}NNa_2O_5$. 1 H_2O requires C, 47.71; H, 4.62; N, 4.28%.

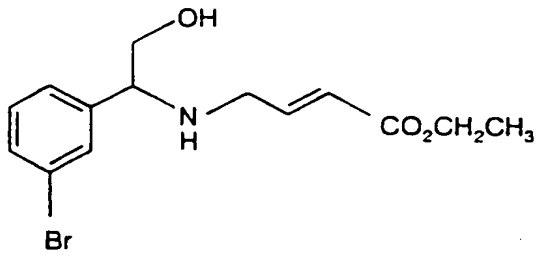
Hydrolysis of the cis-(2S,5S)-enantiomer of Compound 3 diethylester affords the monosodium salt of cis-(2S,5S)-2,5-disubstituted morpholine Compound 4a.

$[\alpha]_D$ = -32.4° (c = 0.39, H_2O).

Found C, 47.90; H, 5.22; N, 4.03%.

$C_{13}H_{14}NNaO_5$. 2 H_2O requires C, 48.30; H, 5.61; N, 4.33%.

Example 4



Compound 5

A solution of 1, 8 - diazabicyclo [5.4.0] undec-7-ene (1.53g, 10mM) in dry THF (4ml) is added dropwise over 1 hour to a cooled (≤ 20°C) solution of Compound C (2.16g, 10mM) and ethyl 4-bromocrotonate (1.39ml, 10mM) in THF (16ml). The resulting mixture is stirred for a further 64 hours at room temperature. The mixture is filtered and the filtrate is evaporated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water then brine and the organic phase is dried over magnesium sulphate, filtered and evaporated under reduced pressure to afford a

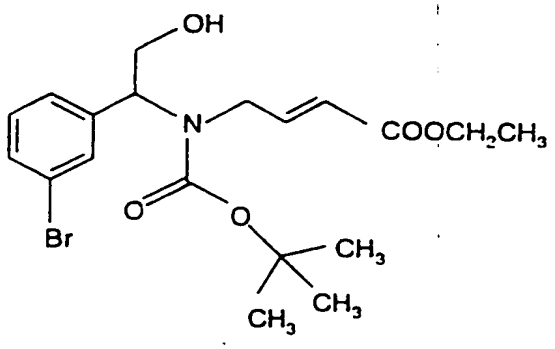
brown oil which is purified by flash chromatography on silica using ethyl acetate: hexane (2:1) as eluant to afford Compound 5.

Found: C, 50.85; H, 5.68; N, 4.15%

$C_{14}H_{18}$ Br NO_3 requires C, 51.23; H, 5.53; N, 4.27%.

^{13}C nmr (100MHz; $CDCl_3$) δ (ppm) 14.12 (q), 47.60 (t), 60.33 (t), 63.56 (d), 66.63 (t), 121.52 (d), 122.74 (s), 125.97 (d), 130.14 (d), 130.26 (d), 130.58 (d), 142.63 (s), 146.28 (d), 166.34 (s).

Example 5



Compound 6

A mixture of Compound 5 (3.0g, 9.14mM) and di-tert-butyl dicarbonate (7.98g, 36.56mM) in dry THF (45ml) is heated under reflux for 6 hours. The mixture is cooled to room temperature and evaporated under reduced pressure to afford a pale yellow oil. The residue is purified by flash chromatography on silica using ethyl acetate: hexane (1:2) as eluant to afford Compound 6.

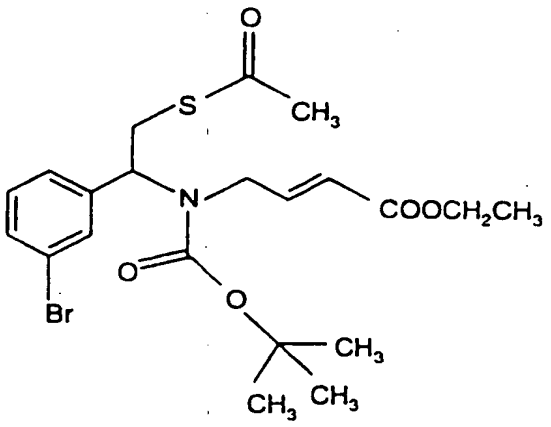
Found: C, 52.81; H, 6.22; N, 3.37%

$C_{19}H_{26}Br$ NO_5 requires C, 53.28; H, 6.12; N, 3.27%.

^{13}C nmr (100MHz; $CDCl_3$) δ (ppm)

14.09 (q), 28.21 (q), 45.99 (t), 60.33 (t), 60.55 (d), 62.39 (t), 81.09 (s), 121.82 (d), 122.66 (s), 126.23 (d), 130.09 (d), 130.72 (d), 130.81 (d), 140.15 (s), 144.51 (d), 152.64 (s), 166.01 (s).

Example 6



Compound 7

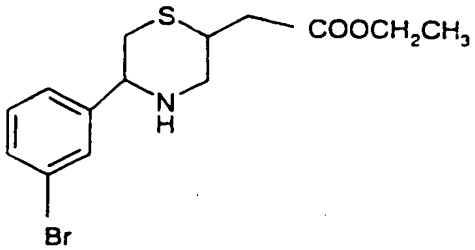
A solution of triphenylphosphine (1.23g, 4.68mM) in dry THF (7.5ml) is cooled to 5°C. A solution of di-iso-propyl-azodicarboxylate (0.946g, 4.68mM) in dry THF (2.5ml) is added dropwise over 5 minutes and the resulting mixture is stirred for 45 minutes at 5°C. A mixture of Compound 6 (1.0g, 2.34mM) and thioacetic acid (0.333ml, 4.68mM) in dry THF (5ml) is added dropwise over 10 minutes. The resulting mixture is stirred for 1 hour at 5°C and then 3 hours at room temperature. The mixture is evaporated under reduced pressure and the residue is purified by flash chromatography on silica using hexane: ethyl acetate (4:1) as eluant to afford Compound 7.

Found: C, 51.66: H, 6.02; N, 3.02; S, 6.29%.

$C_{21}H_{28}Br\ NO_5\ S$ requires C, 51.85; H, 5.80; N, 2.88; S, 6.59%.

^{13}C nmr (100MHz; $CDCl_3$) δ (ppm) 14.10 (q), 28.22 (q), 30.41 (q), 30.70 (t), 45.61 (t), 57.66 (d), 60.23 (t), 80.98 (s), 122.15 (d), 122.66 (s), 126.03 (d), 130.08 (d), 130.56 (d), 131.02 (d), 141.09 (s), 143.98 (d), 155.00 (s), 165.76 (s), 194.79 (s).

Example 7



Cis isomer Compound 8
trans isomer Compound 9

A solution of Compound 7 (500mg, 1.03mM) in absolute ethanol (10ml) is cooled to 5°C and then saturated with hydrogen chloride gas. The resulting mixture is stirred at 5°C for 1 hour and then warmed to 45°C for 3 hours. The mixture is cooled to room temperature and allowed to stand for 20 hours. The mixture is evaporated under reduced pressure and the residue is dissolved in chloroform. The organic phase is washed with saturated $NaHCO_3$ solution, water and brine then dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue is purified by flash chromatography on silica using ether : hexane (1:1) as eluant to afford the cis-2, 5-disubstituted thiomorpholine racemic Compound 8 and trans-2, 5-disubstituted thiomorpholine racemic Compound 9.

Compound 8

^{13}C nmr (100 MHz; $CDCl_3$) δ (ppm) 14.16 (q), 30.78 (t), 33.28 (d), 37.46 (t), 53.23 (t), 60.26 (t), 62.27 (d), 122.61 (s), 125.33 (d), 129.57 (d), 130.11 (d), 130.81 (d), 146.10 (s), 171.84 (s).

Compound 9

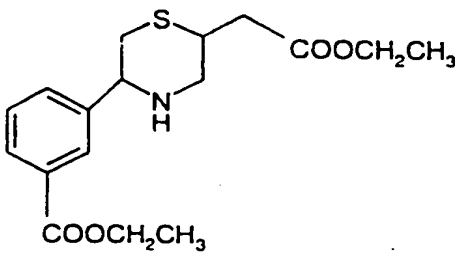
Found: C, 48.84; H, 5.32; N, 3.96; S, 9.32%.

$C_{14}H_{18}Br\ NO_2\ S$ requires C, 48.84; H, 5.27; N, 4.07; S, 9.31%.

^{13}C nmr (100 MHz; $CDCl_3$) δ (ppm)

14.14 (q), 35.64 (t), 36.52 (d), 37.79 (t), 54.56 (t), 60.72 (t), 61.39 (d), 122.57 (s), 125.24 (d), 129.59 (d), 130.10 (d), 130.70 (d), 145.78 (s), 170.55 (s).

Example 8



Cis isomer

Compound 10

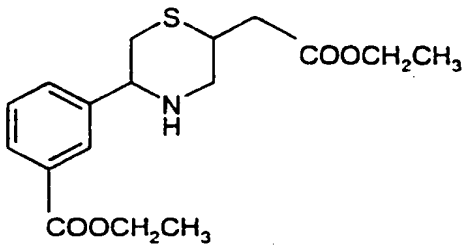
A mixture of Compound 8 (0.19g, 0.552mM) and triethylamine (1ml) in absolute ethanol (25ml) is degassed by sparging with argon for 10 minutes. Bis(triphenylphosphine) palladium (II) chloride

(0.190g, 0.27mM) is added and the mixture is degassed by sparging with argon for a further 10 minutes. The mixture is saturated with carbon monoxide and then pressurised to 20 psi in a pressure vessel. The mixture is slowly heated to 100°C whilst maintaining the pressure below 50 psi for 3 hours. The reaction mixture is cooled to room temperature and allowed to stand for 18 hours. The mixture is filtered and evaporated. The residue is triturated with ethyl acetate and the filtrate is evaporated under reduced pressure. The residue is purified by flash chromatography on silica using ether : hexane (2:1) as eluant to afford the cis-2, 5-disubstituted thiomorpholine racemic Compound 10 as a pale yellow oil.

^{13}C nmr (100 MHz; $CDCl_3$) δ (ppm)

14.16 (q), 14.27 (q), 30.83 (t), 33.33 (d), 37.51 (t), 52.44 (t), 60.48 (t), 60.98 (t), 62.59 (d), 127.56 (d), 128.56 (d), 128.85 (d), 130.72 (s), 131.01 (d), 144.43 (s), 166.53 (s), 171.90 (s).

Example 9



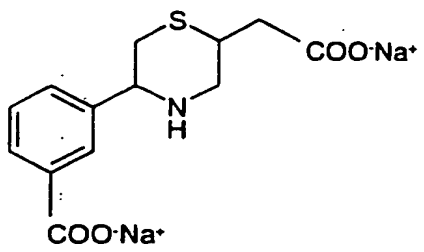
trans isomer

Compound 11

Using substantially the same procedure as described for the preparation of Compound 10, a mixture of Compound 9 (0.50g, 1.45mM), bis(triphenylphosphine) palladium (II) chloride (0.50g, 0.710mM) and triethylamine (1ml) in absolute ethanol (30ml) are reacted under an atmosphere of carbon monoxide (≤ 50 psi) at 100°C for 3 hours. The crude product is purified by flash chromatography on silica using ether: hexane (1:1) as eluant to afford the trans-2, 5-disubstituted racemic Compound 11.

Mass spec. (CI. NH_3) : $(m+1)^+$ m/z 338.

Example 10



Cis isomer

Compound 12

A suspension of Compound 10 (80mg, 0.24mM) in 6M hydrochloric acid (2ml) is heated under reflux for 4 hours. The mixture is cooled to room temperature, filtered and the filtrate is evaporated under reduced pressure. The residue is purified by ion exchange chromatography on Dowex 50 WX 2-200 resin (H^+ form) using 1% sodium hydroxide solution to elute the product. The resulting product is further purified by gel filtration on a BIO-GEL P2 column using water as eluant to afford the cis-2, 5-disubstituted thiomorpholine racemic Compound 12.

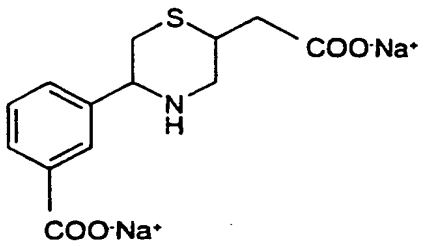
Found: C, 42.73; H, 4.68; N, 3.78%

$C_{13}H_{13}NO_4S.Na_2 . 2.25 H_2O$ requires C, 42.68; H, 4.82; N, 3.83%.

^{13}C nmr (125.8 MHz; D_2O) δ (ppm)

28.23 (t), 33.84 (d), 41.11 (t), 51.37 (t), 60.53 (d), 127.54 (d), 128.57 (d), 129.13 (d), 129.53 (d), 137.24 (s), 142.60 (s), 175.78 (s), 180.59 (s).

Example 11



trans isomer

Compound 13

Using substantially the same procedure as described for the preparation of Compound 12, Compound 11 (200mg, 0.59mM) is reacted in 6M hydrochloric acid (10ml) to afford the trans-2, 5-disubstituted thiomorpholine racemic Compound 13.

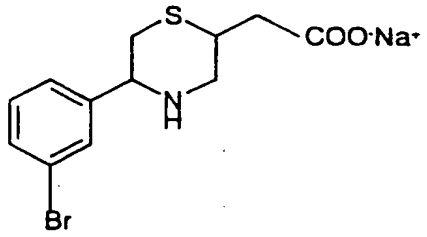
Found: C, 44.25; H, 4.85; N, 3.90%.

$C_{13}H_{13}N\,O_4\,S.\,Na_2\,.\,1.625\,H_2O$ requires C, 44.04; H, 4.62; N, 3.95%.

^{13}C nmr (125.8 MHz; D_2O) δ (ppm)

35.67 (t), 39.08 (d), 43.89 (t), 55.90 (t), 63.64 (d), 129.74 (d), 131.42 (d), 131.67 (d), 132.16 (d), 139.65 (s), 143.90 (s), 177.96 (s), 181.94 (s).

Example 12



trans isomer

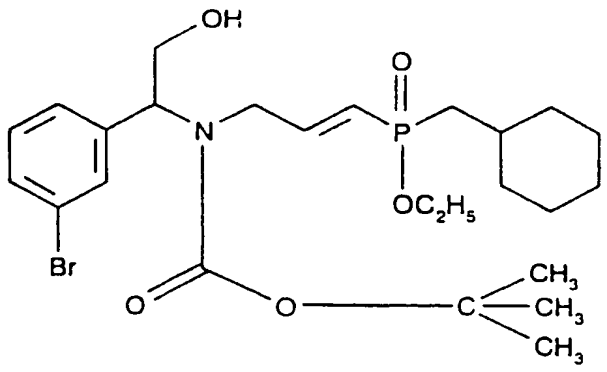
Compound 14

Using substantially the same procedure as described for the preparation of Compound 12, Compound 9 (43mg, 0.125mM) is reacted in 6M hydrochloric acid (1ml) to afford the trans-2, 5-disubstituted thiomorpholine racemic Compound 14.

^{13}C nmr (100MHz; D_2O) δ)ppm

36.29 (t), 39.53 (d), 44.02 (t), 56.25 (t), 63.30 (d), 124.91 (s), 128.15 (d), 132.36 (d), 133.44 (d), 133.59 (d), 147.50 (s), 182.11 (s).

Example 13



Compound 15

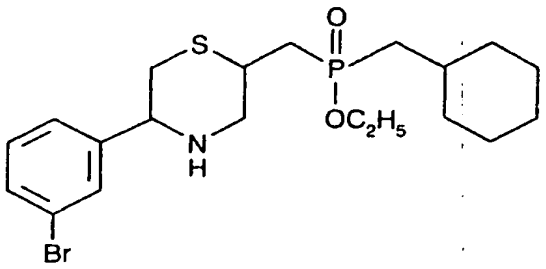
A mixture of Compound F (4.44g, 10.0mM) and di-tert-butyl dicarbonate (8.73g, 40.0mM) in dry THF (75ml) is heated under reflux for 4 hours. An additional aliquot of di-tert-butyl dicarbonate (0.250g, 1.15mM) in THF (5ml) is added and the mixture is heated under reflux for a further 2 hours. The mixture is cooled to room temperature and

allowed to stand for 18 hours. The mixture is evaporated under reduced pressure and the residue is purified by flash chromatography on silica using ethyl acetate as eluant to give Compound 15 as a mixture of phosphorus diastereomers.

Mass spec. (CI, NH_3): $(M+1)^+$ m/z 544 and 546.

^{31}P nmr (162 MHz; $CDCl_3$): δ (ppm) 42.71 (broad).

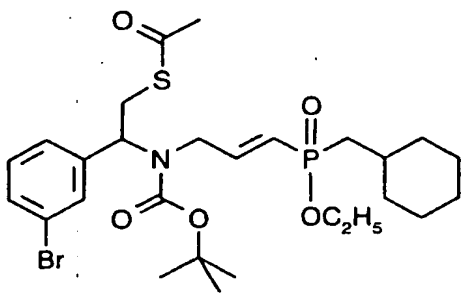
Example 14



Compound 18 (cis)
Compound 19 (trans)

Step 1

A solution of triphenylphosphine (5.06g, 19.3mM) in dry THF (50ml) is cooled to 0°C. A solution of di-iso-propylazodicarboxylate (3.9g, 19.3mM) in dry THF (10ml) is added dropwise over 5 minutes and the resulting mixture is stirred for 45 minutes at 0°C. A mixture of Compound 13 (5.25g, 9.66mM) and thioacetic acid (1.39ml, 19.3mM) in dry THF (15ml) is added dropwise over 10 minutes. The resulting mixture is stirred for 1 hour at 0°C and then 3 hours at room temperature. The mixture is evaporated under reduced pressure and the residue is purified by flash chromatography on silica using ethyl acetate as eluant to afford a mixture of Compound 16 (as a mixture of diastereomers at phosphorus) and triphenylphosphine oxide.

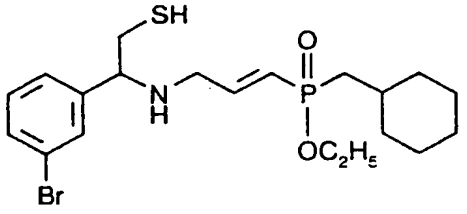


Compound 16

^{31}P nmr (162MHz; $CDCl_3$): δ (ppm) 42.28.

Step 2

The product from step 1 is dissolved in absolute ethanol (100ml). The solution is cooled to 0°C and then saturated with hydrogen chloride gas. The solution is warmed to 45°C for 3 h and then cooled to room temperature. The mixture is evaporated under reduced pressure and the residue is dissolved in ethyl acetate. The organic phase is washed with saturated sodium bicarbonate solution, water, brine then dried over magnesium sulphate filtered and evaporated under reduced pressure. The residue is purified by flash chromatography on silica using ethyl acetate as eluant to afford a mixture of Compound 17 (as a mixture of diastereomers at phosphorus) and triphenylphosphine oxide.



Compound 17

^{31}P nmr (162MHz; $CDCl_3$): δ (ppm) 42.95 and 42.98.

Step 3

The product from step 2 is dissolved in methanol: water (3:1) and purified on a Dowex 50 WX 2-200 (H^+ form) ion exchange column using methanol: water (3:1) to elute triphenylphosphine oxide. Subsequent elution using methanol: water: triethylamine (67.5 : 22.5: 10) affords a residue that is further purified by flash chromatography on silica using 5% methanol in ethyl acetate as eluant to afford cis-2, 5-disubstituted thiomorpholine racemic Compound 18 and trans-2,5-disubstituted thiomorpholine racemic Compound 19 each as a mixture of diastereomers at phosphorus.

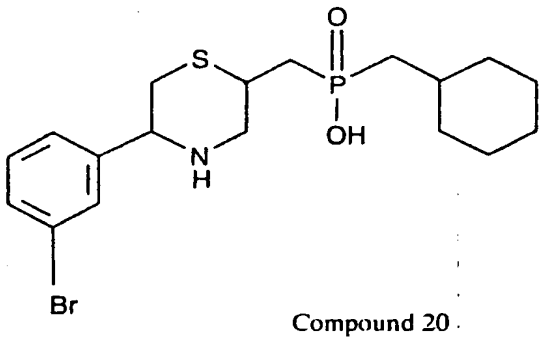
Compound 18

^{31}P nmr (162MHz; $CDCl_3$): δ (ppm) 55.04 and 55.84.

Compound 19

^{31}P nmr (162MHz; $CDCl_3$): δ (ppm) 53.97 and 53.73.

Example 15



Compound 20

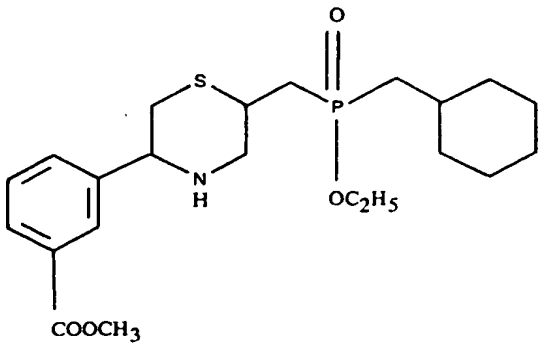
Bromotrimethylsilane (1.0ml, 7.58mM) is added to a solution of Compound 19 (0.125g, 0.27mM) in dry dichloromethane (3ml). The reaction mixture is stirred for 24 hours at room temperature. The mixture is evaporated under reduced pressure and the residue is purified by ion exchange chromatography on Dowex 50 WX 2-200 resin (H^+ form) using triethylamine: methanol: water (10: 45: 45) to elute the product. The resulting product is

dried under high vacuum to afford trans-2,5-disubstituted thiomorpholine racemic Compound 20 is an off white solid.

Found: C, 49.58; H, 6.34; N, 3.13; S, 7.19%.
$C_{18}H_{27}Br\ NO_2PS$ requires C, 50.00; H, 6.30; N, 3.24; S, 7.42%.

^{31}P nmr (202.5MHz; D_2O/NaOD) δ (ppm) 42.91.

Example 16

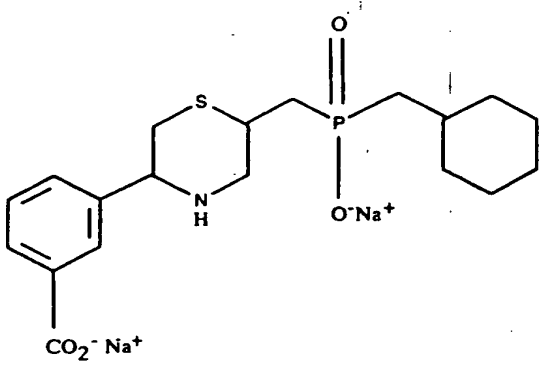


Compound 21

A mixture of Compound 19 (0.20g, 0.43mM) and triethylamine (1ml) in methanol (20ml) is degassed by sparging with argon for 5 minutes. Bis(triphenylphosphine) palladium (II) chloride (0.154g, 0.22mM) is added and the mixture is degassed by sparging with argon for a further 5 minutes. The mixture is saturated with carbon monoxide and then pressurised to 20 psi in a pressure vessel. The mixture is slowly heated to 100°C whilst maintaining the pressure below 50 psi for 4 hours. The mixture is cooled to room temperature, filtered and evaporated. The residue is triturated with ethyl acetate and the filtrate evaporated. The residue is purified by flash chromatography on silica using 5% methanol in ethyl acetate as eluant to afford trans-2, 5-disbustituted thiomorpholine racemic Compound 21 as a mixture of diastereomers at phosphorus.

^{31}P nmr (202.5MHz; $CDCl_3$): δ (ppm) 54.50 and 54.74.

Example 17



Compound 22

Bromotrimethylsilane (0.5ml, 3.79mM) is added to a solution of Compound 21 (0.12g, 0.273mM) in dry dichloromethane (5ml) and the mixture is stirred for 24 hours at room temperature. The mixture is evaporated under reduced pressure and the residue is dissolved in water (10ml). Triethylamine (1ml) is added and the mixture is heated under reflux for 6 hours. The mixture is cooled to room temperature, and the solvent is removed under reduced pressure to afford a residue which is purified by ion exchange chromatography on Dowex 50 WX 2-200 resin (H^+ form) using 2% sodium hydroxide solution: methanol (1:1) to elute the product. The resulting product is further purified by gel filtration on a Bio-Gel P2 column using water as eluant to afford trans-2, 5-disubstituted thiomorpholine racemic Compound 22 as a white solid.

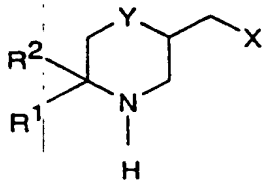
Found: C, 46.46; H, 6.51; N, 2.77; S, 6.30%.
$C_{19}H_{26}NO_4PS.Na_2.2.75H_2O$ requires C, 46.48; H, 6.46; N, 2.85; S, 6.53%.

^{31}P nmr (202.5MHz; D_2O): δ (ppm) 42.75.

^{13}C nmr (100MHz; D_2O): δ (ppm) 28.61 (t), 28.72 (2 x t), 35.29 (d), 36.10 (t), 36.44 (d), 37.17 (t), 37.64 (t), 37.73 (t), 41.55 (t), 57.20 (t), 63.59 (d), 129.84 (d), 131.64 (d), 131.79 (d), 132.19 (d), 139.89 (s), 143.54 (s), 177.88 (s).

Claims

1. A compound of formula



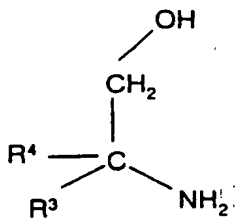
(I)

wherein X is carboxy or a group of formula -PO(OH)-R where R is an unsubstituted or substituted hydrocarbyl group, R^1 is a monovalent aromatic or araliphatic group connected through a carbon atom thereof to the indicated carbon atom, R^2 is hydrogen or an unsubstituted or substituted hydrocarbyl group, and Y is oxygen or sulphur when X is carboxy, or sulphur when X is -PO(OH)-R,
or a salt or ester thereof.

2. A compound according to claim 1, in which Y is as defined in claim 1, X is carboxy, R^1 is phenyl, 3-bromophenyl, 3-iodophenyl, 3,4-dichlorophenyl, 3-cyanophenyl, 3-(methoxycarbonyl)phenyl, 3-(ethoxycarbonyl)phenyl, 3-carboxyphenyl, 3-nitrophenyl, benzyl, 4-iodobenzyl, 4-carboxybenzyl, 4-iodobenzyl, 3-carboxybenzyl, 3-ethoxycarbonylbenzyl, 4-carboxybenzyl, 4-ethoxycarbonylbenzyl or indol-3-yl, and R^2 is hydrogen or isopropyl.

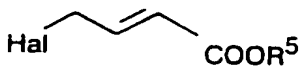
3. A compound according to claim 1, in which Y is as defined in claim 1, X is -PO(OH)-R, R^1 is 3-bromophenyl, 3-(methoxycarbonyl)phenyl or 3-carboxyphenyl, R is cyclohexylmethyl or 4-methoxybenzyl and R^2 is hydrogen.

4. A method of preparing a compound according to claim 1 where X is carboxy and Y is oxygen which comprises reacting a compound of formula



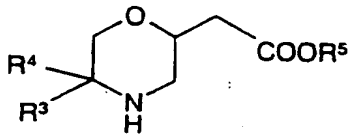
II

where R^3 is R^1 as defined in claim 1 with the proviso that R^3 is not substituted by carboxyl, and R^4 is R^2 as defined in claim 1 with the proviso that R^4 is not substituted by carboxyl, with a compound of formula



III

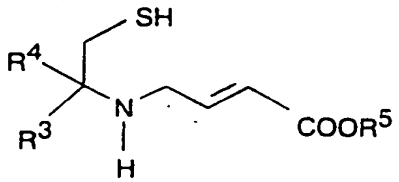
where Hal is halogen and R^5 is C_1 to C_8 alkyl, in the presence of a base to give a compound of formula



IV

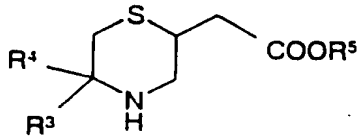
where R^3, R^4 and R^5 are as defined above, followed, where required, by one or more substitution reactions to change the nature of a substituent in R^3 and/or R^4 and/or by hydrolysis of an ester substituent in R^3 and/or R^4 to carboxyl and/or by hydrolysis of the ester group -$COOR^5$ to carboxyl.

5. A method of preparing a compound according to claim 1 where X is carboxy and Y is sulphur which comprises reacting a compound of formula



IX

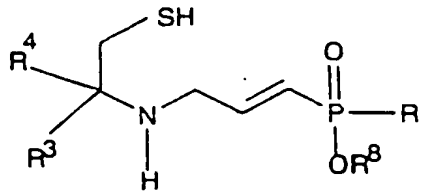
where R^3, R^4 and R^5 are as defined in claim 4, with an acid or with a base to give a compound of formula



X

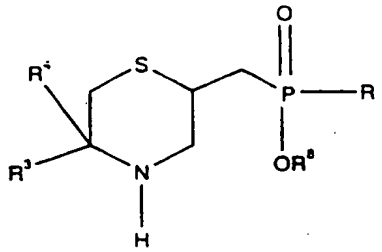
where R^3, R^4 and R^5 are as defined in claim 4 followed, where required, by one or more substitution reactions to change the nature of a substituent in R^3 and/or R^4 , and/or by hydrolysis of an ester substituent in R^3 and/or R^4 to carboxyl and/or by hydrolysis of the ester group - $COOR^5$ to carboxyl.

6. A method of preparing a compound according to claim 1 where X is -PO(OH)-R and Y is sulphur which comprises reacting a compound of formula XIII



XIII

where R is as defined in claim 1, R^3 and R^4 are as defined in claim 4 and R^8 is C_1-C_8 alkyl, with a base, to give a compound of formula XIV



XIV

where R, R^3, R^4 and R^8 are as defined above, followed, where required, by one or more substitution reactions to change the nature of a substituent in R^3 and/or R^4, and/or by hydrolysis of an ester substituent in R^3 and/or R^4 to carboxyl and/or by conversion of the ester group $-OR^8$ to -OH.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1 to 3, optionally together with a pharmaceutically acceptable carrier.

8. A compound according to any of claims 1 to 3 for use as a pharmaceutical.

9. A compound according to any of claims 1 to 3 for use in the treatment or prevention of a condition characterized by stimulation of a $GABA_B$ receptor.

10. Use of a compound according to any of claims 1 to 3 in the preparation of a medicament for the treatment or prevention of a condition characterised by stimulation of a $GABA_B$ receptor.

11. A method of treating or preventing a condition in a warm-blooded mammal characterised by stimulation of $GABA_B$ receptor which comprises administering to the mammal a compound according to any of claims 1 to 3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/E. 97/07235

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07F 9/6533, C07F 9/6544, C07D 265/30, C07D 279/12, A61K 31/535, A61K 31/54
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07F, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9422843 A1 (SCHERING CORPORATION), 13 October 1994 (13.10.94) --	1-10
P,X	WO 9709335 A1 (CIBA-GEIGY AG), 13 March 1997 (13.03.97) --	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1998	25. 05. 98

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GÖRAN KARLSSON

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/07235

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ›nal application No.
PCT/EP 97/07235

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9422843 A1	13/10/94	AT 160143 T	15/11/97
		AU 6408894 A	24/10/94
		CA 2158952 A	13/10/94
		DE 69406779 D,T	12/03/98
		EP 0690850 A,B	10/01/96
		IL 109111 D	00/00/00
		JP 8503229 T	09/04/96
		ZA 9402090 A	26/09/94
WO 9709335 A1	13/03/97	AU 6831996 A	27/03/97
		GB 9518186 D	00/00/00
		GB 9613047 D	00/00/00